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FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
GODDARD, LAURA B	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/816,698
Filing Date: April 02, 2004
Appellant(s): HUNG ET AL.

Melissa L. Sistrunk
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 14, 2007 appealing from the Office action mailed October 31, 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

No evidence is relied upon by the examiner in the rejection of the claims under appeal.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(A) Claims 12, 14-16, 18-26, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement in that the specification does not describe a mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}, that is required for inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. This written description rejection is set forth in the Office Action mailed October 31, 2006, section 3, pages 2-7.

As set forth therein, Examiner provides reasons why the teachings of the specification do not provide an adequate written description of the claimed invention:

The claims are drawn to a mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}, wherein the mutant Bik polypeptide induces anti-tumor activity, anti-

cell proliferation activity, and/or pro-apoptotic activity in a subject. According to the specification, a mutant Bik polypeptide comprises at least one altered amino acid compared to native Bik and the alteration of Bik may comprise a modified amino acid or substituted amino acid (p. 7, [18]). The specification discloses that mutations, either to similar amino acids or not, may be made anywhere in the Bik polypeptide and that some of these mutants will have the same activity as the exemplary embodiments provided in the specification. For example, threonine, serine, or other appropriate amino acids anywhere within Bik can be substituted (p. 9, [23]). The specification discloses exemplary Bik polypeptides SEQ ID NO:3 and SEQ ID NO:4 (p. 9) and mutant Bik SEQ ID NO:9, which comprises the same sequence as SEQ ID NO:3 except it comprises the Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitutions (p. 9 and 16). The specification does not disclose any other mutant Bik polypeptides having an altered amino acid sequence relative to SEQ ID NO:3 that comprises at least any amino acid mutation at position 33 and 35, any mutant Bik having any altered amino acid sequence in addition to having Thr^{33} to Asp^{33} and Ser^{35} to Asp^{35} substitutions, or any mutant Bik polypeptide comprising any modification at position 33 and 35 that results in an inability of the amino acid to be phosphorylated, as broadly encompassed in the claims.

The specification as originally filed does not provide an adequate written description of "a mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}, wherein the mutant Bik polypeptide induces anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject" critical to the claimed invention because the specification

does not meet the standards as set forth in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) or Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002) because:

(a) Lilly requires that written description of an invention involving a chemical genus, like a chemical species, requires a precise definition such as by structure, formula, [or] chemical name, of the claimed subject matter sufficiently to distinguish it from other materials. Further the court also stated that "A definition by function...does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is." Finally, the court found that description of the genus claimed may be achieved by means of a recitation of a representative number of molecules, defined by sequence which fall within the scope of the genus or a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. In the instant case, the broadly claimed genus is not defined by a precise definition structure, formula, [or] chemical name, of the claimed subject matter sufficiently to distinguish it from other materials, the broadly claimed genus is defined only by an undefined structure, that is a mutant Bik polypeptide having *any* altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}, and the function of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject, and only a single representative of the genus, SEQ ID NO:9, is disclosed. Thus the instant specification does not meet the written description standard for the "mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that

comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}" critical to the claimed invention as set forth in Lilly;

(b) Enzo further clarified the written description requirement, indicating that a molecule can be adequately described without disclosing its complete structure. The Enzo court adopted the standard that the written description requirement can be met by disclosure of sufficiently detailed, relevant identifying characteristics, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure. In the instant case, the specification provides no known or disclosed correlation between the undefined altered amino acid sequence of a mutant Bik polypeptide, relative to SEQ ID NO:3 and comprising any substitution at least at a mutation at Thr^{33} and Ser^{35} and the function of the broadly claimed genus, that is inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. Thus, the instant specification does not meet the written description standard for the "mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}" critical to the claimed invention as set forth in Enzo.

Given that the specification does not meet the written description standards of either Lilly or Enzo for the mutant Bik polypeptide, the specification does not provide an adequate written description of the claimed method of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject because since the specification fails to adequately describe the product which is critical to the claimed invention, it also fails to adequately describe the claimed method.

(B) Claims 12, 14-16, 18-26, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This enablement rejection is set forth in the Office Action mailed October 31, 2006, section 5, pages 9-15.

As set forth therein, Examiner reviews the teachings of the specification and provides reasons why the teaching cannot be extrapolated to the enablement of the claims as follows:

The claims are drawn to a method of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject, comprising administering to the subject a mutant Bik polypeptide having an altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}, wherein the mutant Bik polypeptide induces anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in the subject (claims 12, 19-23, 25, 26), wherein the substitution is a Thr^{33} to Asp^{33} or Ser^{35} to Asp^{35} substitution (claims 14 and 15), wherein the polypeptide further comprises a transduction domain (claims 16), the method of claim 12 further defined as comprising modifying the Bik polypeptide at amino acid position 33, amino acid position 35, or both, wherein the modification results in an inability of the amino acid to be phosphorylated (claim 42).

According to the specification, a mutant Bik polypeptide comprises at least one altered amino acid compared to native Bik and the alteration of Bik may comprise a

modified amino acid or substituted amino acid (p. 7, [18]). The specification discloses that mutations, either to similar amino acids or not, may be made *anywhere* in the Bik polypeptide and that some of these mutants will have the same activity as the exemplary embodiments provided in the specification. For example, threonine, serine, or other appropriate amino acids anywhere within Bik can be substituted (p. 9, [23]). The specification contemplates methods for inhibiting proliferation in a cancer and/or tumor cell comprising contacting the cell with a mutant Bik polypeptide in an amount effective to inhibit cellular proliferation (p. 3, p. 10-11, and Example 12, p. 86). The specification discloses substituting Bik residues Thr^{33} and Ser^{35} with aspartate (Examples 1 to 3, and 6) to produce a mutated Bik *nucleic acid* for inoculation of the nucleic acid into mice with successful results *in vivo* to reduce tumor volume and *in vitro* to induce apoptosis.

One cannot extrapolate the disclosure of the specification to the enablement of the claims because the claims are broadly drawn to a genus of mutant Bik polypeptides having any altered amino acid sequence, relative to SEQ ID NO:3, that comprise a substitution at least at a mutation at Thr^{33} and Ser^{35} or further comprising a protein transduction domain, wherein it cannot be predicted that the broad genus of mutant Bik polypeptides will function as claimed. Further, one cannot extrapolate the disclosure of the specification to the enablement of the claims because the specification does not provide examples for predictably inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity *in vivo*, which is unpredictable in the art.

The claimed invention is drawn to administering mutant Bik *polypeptides* to a subject. Examiner carefully reviews the art with regards to the function of Bik *in vivo* and the unpredictability of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity *in vivo* comprising administering the mutant Bik polypeptide as claimed.

Mathai et al (J of Biological Chemistry, 2005, 280, 23829-23836) teach that Bik is located at the endoplasmic reticulum from where it elicits pro-apoptotic signals and, given sufficient time, these signals lead to cell death by pathway(s) (p. 23835). Clearly, Bik can only initiate apoptosis if it is inside the cell. Given that Bik requires intracellular initiation of apoptosis, one could not predictably induce apoptosis by administration of a mutant Bik polypeptide to a cell because the polypeptide would be external to the cell and unable to induce apoptosis.

More factors must be considered in addition to internalizing a protein when administering to a cell to induce pro-apoptotic activity, anti-cell proliferation activity, or exert anti-tumor effects. One factor is targeting the protein to a specific tissue or cell type such as a tumor cell so that surrounding normal tissues are not damaged by the protein's effects. Another factor to consider is the development of an immune response against a mutant polypeptide that is not found naturally occurring in an animal. Administration of an unnaturally occurring protein may induce an immune response against the protein and prevent the protein from reaching its target. Azar et al teach (Apoptosis, 2000, 5:531-542), that the design of specific targeting reagents/drugs still remains the major goal in the treatment of neoplastic diseases and the main aim is to

direct therapeutic agents into tumor cells, while avoiding damage to normal tissues and without evoking an immune response (p. 531, col. 1). Azar et al teach the successful targeting of a chimeric Bik protein joined to Gonadotropin releasing hormone (GnRH) that targets adenocarcinomas. Targeting Bik to the cells induced apoptosis *in vitro* in adenocarcinoma cell lines (abstract, p. 533, col. 2; p. 541, col. 2).

Azar et al address the problems of administering their chimeric Bik protein *in vivo*. The reference teaches that the immunogenicity of targeting proteins constitutes a problem to which no practical solution has been found. Azar et al teach that human chimeric proteins that incorporate a human apoptosis-inducing agent, such as Bik, may decrease immunogenicity problems because the apoptosis-inducing agent is of human origin is expected to display reduced immunogenicity in recipients (p. 539, col. 1 and 2; p. 541, col. 2). However, the claims are drawn to a mutant Bik polypeptide that is *not* the wild-type form and the mutant form may elicit an immune response against the polypeptide, hence, clearing the polypeptide from the animal's body and preventing it from functioning. Given the teaching of Azar et al and Mathai et al, one of skill in the art could not predictably induce pro-apoptotic activity, anti-cell proliferation activity, or anti-tumor activity by administering the mutant Bik polypeptide to a subject as claimed.

The claimed invention is drawn to administering a broad genus of mutant Bik polypeptides having any altered amino acid sequence, relative to SEQ ID NO:3, that comprise a substitution at least at a mutation at Thr^{33} and Ser^{35} or further comprising a protein transduction domain, wherein it cannot be predicted that the broad genus of mutant Bik polypeptides will function as claimed.

Examiner provided reasons for why one of skill in the art could not predictably induce pro-apoptotic activity, anti-cell proliferation activity, or anti-tumor activity *in vivo* comprising administering a broad genus of mutant Bik polypeptides comprising *any* altered amino acid sequence relative to SEQ ID NO:3, in addition to *any* substitution at positions Thr^{33} and Ser^{35}. Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape of a protein and determines the ability of said protein to fold into unique three-dimensional structures that allows them to function. Bowie et al further teach that certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (p. 1306, cols 1 and 2). Clearly, the three dimensional structure of a protein is critical to its function, particularly relating to the induction of pro-apoptotic activity, anti-cell proliferation activity, or anti-tumor activity. However, neither the specification nor the art of record provide teachings that provide information about the effects any altered amino acid sequence relative to SEQ ID NO:3 and any amino acid substitution at positions Thr^{33} and Ser^{35} would have on the activity of a mutant Bik polypeptide. This information appears to be critical because the art recognizes (see Bowie et al above) that it is the protein sequence that determines the three dimensional shape of a protein and suggests that the three-dimensional structure of the protein molecule may be essential for the protein's function and ability to be modulated. Thus, in the absence of guidance in the specification, the effects of the undefined amino acid substitutions, it cannot be predicted and one could not determine how to practice the claimed invention or predict

which of the whole universe of broadly claimed mutant Bik polypeptides having any altered amino acid sequence relative to SEQ ID NO:3 and comprising any substitution at positions Thr^{33} and Ser^{35} would function as claimed with a reasonable expectation of success.

(10) Response to Argument

(A) With regards to claims 12, 14-16, 18-26, 41 and 42 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, Appellant argues that there is adequate written description for all of the mutant Bik molecules encompassed by the claims and states claim 12. Appellant states that support for claim 12 can be found in the specification as follows: (i) the specification discloses the sequence of Bik polypeptide in SEQ ID NO:3; (ii) the specification discloses the exemplary mutant Bik polypeptide in SEQ ID NO:9; (iii) the specification discusses the generation of mutations in Bik; (iv) the specification provides exemplary codons for the mutation in Table 1; and (v) the specification teaches biologically functional equivalents of mutant Bik. Appellant argues that the specification discloses the relevant, identifying characteristics (i.e., structure or other physical and/or chemical properties) of the claimed invention.

The arguments have been considered but are not found persuasive because neither the specification nor the claims identify the critical structure required for the genus of mutant Bik polypeptides claimed to function in inducing pro-apoptotic activity, anti-cell proliferation activity, or anti-tumor activity in a subject. The claims are broadly

drawn to a mutant Bik polypeptide having *any* altered amino acid sequence, relative to SEQ ID NO:3, that comprises a substitution at least at a mutation at Thr^{33} and Ser^{35}. With regards to (i): the disclosure of SEQ ID NO:3 does not provide the critical structure of a mutant Bik polypeptide that functions induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject; (ii) exemplary mutant Bik SEQ ID NO:9 is not adequate representation of the broad genus of mutant Bik polypeptides having *any* altered amino acid sequence, relative to SEQ ID NO:3, in addition to mutations at Thr^{33} and Ser^{35} that also function as claimed; (iii) and (iv) the knowledge of generating mutations and exemplary codons do not provide the critical structures required for a mutant Bik to function as claimed and to distinguish the broadly claimed genus of polypeptides; and (v) disclosure of biologically functional equivalents of mutant Bik still do not provide the critical structures required for a mutant Bik to function as claimed and to distinguish the broadly claimed genus of polypeptides.

Appellants argue that Examiner appears to misapply the written description requirement as set forth in Lilly and Enzo which are recited on page 4 of the Final Office Action. Appellant argues that the claims of the present application recite more than a mere function. Lilly requires only that claims to genetic material require recitation of more than mere function. Appellant argues that current claim 1 (Examiner assumes Appellant intended to state "claim 12" since claim 1 was canceled), for example, recites that the polypeptide sequence is relative to SEQ ID NO:3 and that there are substitutions at Thr^{33} and Ser^{35}. Appellants argue that they provide a reference Bik

sequence, SEQ ID NO:3, to give the skilled artisan disclosure of exemplary structure and that also provide functional characteristics by reciting that the mutant Bik polypeptide induces anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity.

The argument has been considered but is not found persuasive because the specification and claims do not identify the required structure for a mutant Bik polypeptide to function in inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. Lilly states that a precise definition structure, formula, [or] chemical name, of the claimed subject matter may sufficiently distinguish it from other materials, however, the claimed mutant Bik polypeptide comprises an unknown amino acid structure having *any* mutations relative to SEQ ID NO:3 and only mutations at Thr^{33} and Ser^{35}, of which, fails to disclose identifying, structural features common to the members of the genus that would function to induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. While Appellants reference the mutant Bik to SEQ ID NO:3, the claimed mutant Bik still comprises any unknown amino acid sequence relative to SEQ ID NO:3 because it broadly encompasses any mutations relative to SEQ ID NO:3 and is not required to comprise any structures of SEQ ID NO:3.

Appellants argue that they have met the standards of Enzo because the claims provide specific mutations at amino acids Thr^{33} and Ser^{35} that allow the polypeptide to induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity.

Appellants argue that the remainder of the mutant Bik polypeptide other than Thr^{33} and Ser^{35} finds guidance in the specification in reference to SEQ ID NO:3 and in Table 1 which provides codons for all standard amino acids.

The arguments have been considered but are not found persuasive because neither the claims nor the specification teach the amino acids critical to the function, *i.e.*- anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity *in vivo* of the broadly claimed mutant Bik polypeptides.

Appellant argues that they have provided a representative number of mutant Bik polypeptides having a mutation at Thr^{33} and Ser^{35} because they have provided SEQ ID NOs:9 (comprises mutations at Thr^{33} and Ser^{35}), 7 (comprises mutation at Thr^{33}), and 8 (comprises a mutation at Ser^{35}), although SEQ ID NOs:7 and 8 are drawn to non-elected species. Appellants argue that Examiner ignores that Appellants have provided sufficient guidance to anyone of skill in the field to employ a representative Bik sequence as a reference for other mutations and have shown possession of such an invention by providing routine methods how to generate and characterize such mutants for the intended activity.

The arguments have been considered but are not found persuasive because there is a disclosure in the specification of broad definitions for the mutant Bik polypeptide genus as encompassing any mutation and any unknown structure (p. 7, [18]; p. 9, [23]). However, despite the disclosure of representative species of mutant Bik polypeptides (i.e. SEQ ID NO:9 which is actually SEQ ID NO:3 with specific amino acid

substitutions at positions Thr^{33} and Ser^{35}), the specification still provides a definition of the mutant Bik polypeptide genus that encompasses any protein with any mutation of any unknown structure. There is no recitation or disclosure of structural features common to the members of the mutant Bik polypeptide genus or which features constitute a substantial portion of the genus. While the claims reference SEQ ID NO:3, the claimed mutant Bik polypeptide is not required to comprise any structures of SEQ ID NO:3.

Again, although the specification discloses specific SEQ ID NOs of mutant Bik polypeptides that have very specific functions of inducing anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity *in vivo*, and although the specification discloses methods for generating mutations and screening for polypeptide activities, neither the claims nor the specification teach the amino acids critical to the claimed function of the broad genus of mutant Bik polypeptides.

(B) With regards to the rejection of claims 12, 14-16, 18-26, 41 and 42 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, Appellant argues that Examiner has failed to establish a *prima facie* case for lack of enablement. Appellant argues that claim 12 recites mutations at specific sites in the Bik polypeptide relative to SEQ ID NO:3 which is disclosed in the specification and that the specification discloses that the mutant Bik polypeptides of the scope of the claims induce anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity in a subject. Appellants argue that no more than routine screening would be required to

practice the full scope of the claimed invention and that enablement under 35 USC 112 is not precluded by the necessity for some experimentation such as routine screening (*in re Wands*). Applicants argue that methods of mutagenesis are well known in the art and are taught in the specification. Appellants argue that one of ordinary skill in the art would be able to, for example, mutate a nucleic acid sequence encoding the Bik polypeptide of SEQ ID NO:3 to have a mutation in Thr^{33} and Ser^{35}. Applicants further argue that those of ordinary skill in the art would be able to make substitutions that are either more or less conservative based on the hydropathic index of the amino acids based on teachings in the specification.

The arguments have been considered but are not found persuasive because the specification and the claims do not provide the structural features common to the members of the mutant Bik polypeptide genus or which features constitute a substantial portion of the genus or that are critical for the claimed polypeptide function, hence one of skill in the art would not know how to make and use a mutant Bik polypeptide that would predictably function as claimed. Even armed with knowledge for generating mutations and the hydropathic index of the amino acids, given the broad genera of mutant Bik polypeptides encompassed by the claims and given the teachings of Bowie et al (above), it is clear that one could not predictably distinguish between those polypeptides that will function as claimed and those that will not, therefore one is left with random experimentation in order to determine which of the broadly claimed mutant Bik polypeptides will function as claimed. Random experimentation is undue.

Appellants argue that the specification provides guidance for administering a mutant Bik polypeptide by teaching two routes of administration of mutant Bik polypeptides: 1) in liposomes and 2) with protein transduction domains.

The arguments have been considered but are not found persuasive because Examiner was clearly addressing guidance for administering a mutant Bik polypeptide to a subject that *functions to successfully induces anti-tumor activity, anti-cell proliferation activity, and/or pro-apoptotic activity as claimed* (see Final Office Action, p. 11), not addressing guidance on *how* to administer a Bik polypeptide.

Appellants argue that Examiner uses the Azar, Mathai and Bowie references (p. 11013 of Final Office Action) as if the skilled artisan were not already aware of such issues, yet the effectiveness of the composition in relation to its cellular targeting and subcellular localization, immunogeneicity, and folding issues, are all routine considerations to one of skill in the art. Appellants argue that the courts have determined that it is not required to disclose well known techniques or scientific principles to those of skill in the art, therefore it was not necessary for Appellants to disclose the routine concerns of cellular targeting and subcellular localization, immunogenicity, and proper folding.

The arguments have been considered but are not found persuasive because each of the references, Azar, Mathai and Bowie, were presented as teachings in the art, the state of the art, and the unpredictability in the art that all contribute to the unpredictability of the invention functioning as claimed, which in turn, all support undue

experimentation to practice the invention as claimed. Each reference is very important in pointing out the unpredictability in the art: 1) Bowie: proteins of unknown and altered structure such as the broadly claimed mutant Bik polypeptides would not predictably function as claimed; 2) Mathai: the Bik polypeptide functions intracellularly, hence extracellular administration of a mutant Bik polypeptide would not predictably function as claimed; and 3) Azar: the unpredictability of Bik polypeptides functioning *in vivo*.

Appellants argue that the courts have determined that experimentation may be considerable in quantity if it is routine. Appellants argue that it is routine in the art to employ standard methods to characterize drug compositions, even though these methods may be considered lengthy. As has been determined by the courts, the scope of the enablement must only bear a "reasonable correlation" to the scope of the claims (*In re Fisher*). Appellants argue that even if experiments are necessary for mutant Bik polypeptides, a considerable amount of routine experimentation is permissible, especially where the Appellants' specification provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed. Appellants argue that time-consuming experiments are acceptable if the type of experiment is standard in the art. An extended period of experimentation for mutant Bik polypeptides may not be undue of the skilled artisan is given sufficient direction or guidance. Appellants argue that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*In re Wands, In re Certain Limited-Charge Cell Culture Microcarriers*).

The arguments have been considered but are not found persuasive. The claims are not drawn to routine characterization of drug compositions, as Appellants argue, they are drawn to inducing anti-tumor activity, anti-cell proliferation activity, and/or anti-apoptotic activity *in vivo*. Examiner disagrees that the experimentation to practice the claimed invention *in vivo* is routine and not undue. The specification does not provide sufficient guidance nor direct one of skill in the art to inducing anti-tumor activity, anti-cell proliferation activity, and/or anti-apoptotic activity *in vivo* without undue experimentation because the specification and the claims do not provide the structural features common to the members of the mutant Bik polypeptide genus or which features constitute a substantial portion of the genus or that are critical for the claimed polypeptide function, hence one of skill in the art would not know how to make and use a mutant Bik polypeptide that would predictably function as claimed. Given the broad genus of mutant Bik polypeptides encompassed by the claims and given the teachings of Bowie et al (above), it is clear that one could not predictably distinguish between those polypeptides that will function as claimed and those that will not, therefore one is left with random experimentation in order to determine which of the broadly claimed mutant Bik polypeptides will function as claimed. Random experimentation is undue. The scope of the enablement does not bear a "reasonable correlation" to the scope of the claims because the claims are broadly drawn to administering mutant Bik polypeptides of unknown structure and are drawn to administering polypeptides that would not predictably function as claimed for the reasons set forth above (see Bowie, Azar, and Mathai above).

Appellants reiterate arguments from the response file August 2, 2006 that the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art (*In re Fisher*), and guidance is not necessary to those skilled in the art, particularly when it is well-recognized that the skill in the art of molecular biology is quite high (*Ex part Forman*). Appellants argue that they have provided sufficient detail by providing an exemplary mutant Bik polypeptide (SEQ ID NO:9), exemplary administration routes, and exemplary reference sequences for the polypeptide sequence outside of the mutations at Thr^{33} and Ser^{35}, exemplary codons for particular amino acids for the polypeptide sequence outside of the mutations at Thr^{33} and Ser^{35}, and description of delivery and treatment protocols for utilizing mutant Bik polypeptides, therefore it would not be undue experimentation to make and use the invention.

The arguments have been considered but are not found persuasive. Each of these arguments has been addressed above. To reiterate, the specification and the claims do not provide the structural features common to the members of the mutant Bik polypeptide genus or which features constitute a substantial portion of the genus or that are critical for the claimed polypeptide function, hence one of skill in the art would not know how to make and use a mutant Bik polypeptide that would predictably function as claimed. While the claims reference Bik polypeptide SEQ ID NO:3, the claimed mutant Bik polypeptides are not required to comprise any structures of SEQ ID NO:3. Further, the amount of knowledge in the state of treating tumors *in vivo* using mutant Bik polypeptides is not high, and the specification does not provide sufficient guidance for

inducing anti-tumor activity, anti-cell proliferation activity, and/or anti-apoptotic activity *in vivo* administering mutant Bik polypeptides that would predictably function as claimed. For the reasons set forth above, the claimed invention would require undue experimentation.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Laura B. Goddard
Art Unit 1642

Conferees:

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Shanon Foley
SPE
1642

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Gary Nickol
SPE
1646